but also that it does not convert to **7**.

We believe that these results strongly indicate that a bis(alkylidene)silacyclopropane intermediate like **4** is present in this reaction sequence. (*Mono*alkylidene)silacyclopropanes have been recently prepared and characterized as stable molecules.[14] Among other interesting reactions, these compounds react quantitatively with methanol to give (allyl)methoxysilanes by cleavage of the Si–C(alkenyl) intraring bond or the (alkylidene)silacyclopropane.[14] The same mechanism is postulated above for the conversion of **4** to **6**. We have also demonstrated the utility of having a PtL₂ substituent present in silacyclic systems to stabilize internally products obtained from chemically initiated, ring-opening reactions. This latter observation might have general application to

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Interaction of Zn^{2+}, Cd^{2+}, and Hg^{2+} with 2-(α-Hydroxybenzyl)thiamin and 2-(α-Hydroxy-α-cyclohexylmethyl)thiamin. Crystal Structure of the Complex Hg(2-(α-hydroxybenzyl)thiamin)Cl₃·H₂O

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Abstract: The reactions of ZnCl₂, CdCl₂, and HgCl₂ with the "active aldehyde derivatives" of thiamin, 2-(α-hydroxybenzyl)thiamin (HBT) and 2-(α-hydroxycyclohexylmethyl)thiamin (HCMT) were studied in methanolic and aqueous solutions. Complexes of the formulas M(HBT)Cl₃ and M(HCMT)Cl₃, (M = Zn^{2+}, Cd^{2+}, Hg^{2+}) were isolated and characterized as solid adducts with elemental analyses, conductivity measurements, and IR spectra. The crystal structure of the complex Hg(HBT)Cl₃ was also solved. The compound is monoclinic ($P2_{1/n}$) with $a = 9.588$ (6) Å, $b = 7.644$ (3) Å, $c = 31.412$ (20) Å, $\beta = 90.41$ (5)°, $V = 2302$ (2) Å³, and $Z = 4$. The HBT ligand is found in the S conformation, as expected for C(2)-substituted derivatives of thiamin, with $\phi_P = 172.7°$ and $\phi_T = -100.0°$. It is concluded from the IR spectra that all the isolated complexes are isostructural and in the same S conformation, as in the compound Hg(HBT)Cl₃, in the solid state. The facile formation of complexes of bivalent metals with the active aldehyde derivatives of thiamin, which contain direct metal–ligand (M–N(1′)) bonding, may indicate that the intervention of metal ions could follow the formation of these intermediates in the enzymatic action of thiamine.

Introduction

The pyrophosphate ester of thiamin (TPP) is the coenzyme for the enzymes carboxylase, pyruvic dehydrogenase, transketolase, and phosphoketolase that catalyze either the decarboxylation of α-keto acids or the formation of α-ketols.[1] For its catalytic action, a bivalent metal ion such as Mg^{2+} is required.[1,2] Other bivalent metal ions such as Co^{2+}, Zn^{2+}, Mn^{2+}, and Cd^{2+} have also been shown to catalyze the various enzymatic reactions in vitro,[1] but not as efficiently as Mg^{2+}.

It is known today that the mechanism of action of TPP involves the formation of the so-called "active aldehyde" intermediates (I) formed with subsequent ionization of a proton from the C(2) atom of the thiazole ring.[3] However, the role played by the bivalent metal ion is not yet clear.[4]

It was proposed that the metal ions are used to bind the coenzyme to the apoenzyme, either through the N(1′) atom of the pyrimidine ring,[5] or through the pyrophosphate group.[6] The N(1′)

I
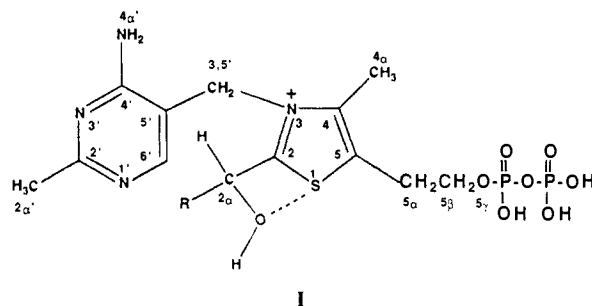
of the pyrimidine moiety was also proposed to coordinate with the metal ion indirectly through a water molecule and simulta-

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neously with the phosphate group.[6b–d] Attempts to prepare complexes of bivalent metals with thiamin and its phosphate esters, in order to recognize the metal binding site, resulted instead in the formation of ionic salts of the type $[L]^{2+}[MX_4]^{2-}$, $[L]^{2+}$-$([MX_3]^-)_2$, or $([L]^+)_2[MX_4]^{2-}$ in most cases.[7] This result is due to the net positive charge located at the N(3) atom and the pK_a value of the N(1') of pyrimidine,[8] which is ~5. The decomposition of the molecule[1] with subsequent ionization of a proton from the C(2) position at pH >7 allows the easy formation of a thiaminium dication (L^{2+}) in acidic media (pH <5), while the monocationic form exists in weakly acidic media (5 < pH < 7). The formation of ionic salts thus takes place easily in aqueous solutions.

Nevertheless, the Pt^{2+} and Pd^{2+} complexes of thiamin and its phosphate esters[9] were the first examples isolated as solid adducts, containing a direct metal–ligand bonding to the N(1') site of the pyrimidine moiety. The subsequent crystal structure determination of the compound Pt(thiamine)Cl₃·H₂O provided unambiguous evidence for the proposed structure.[7h] In addition to the aforementioned crystal structure of thiamin with Pt^{2+}, there exist today five other crystal structure determinations of the ligand and its derivatives, containing similar bonds,[10] namely, with Cu^+, Rh^{2+}, Zn^{2+}, and Cd^{2+}. Bonding to the phosphate group of TPP was observed only in the case of Cu^{2+}.[6e] Finally, in the crystal structure of a complex of Co^{2+} with tetrahydrothiamin, Co–N(1') bonding from metal to the pyrimidine ring was again found.[11]

In the so-called active aldehyde derivatives of thiamin, the positive charge on N(3) has been shown to be partially delocalized with the sulfur atom, which in turn interacts with the oxygen atom of the substituent at C(2)[12] (S···O <3 Å). Because of its importance as an intermediate in the activity of thiamin-dependent enzymes, we decided to try to prepare metal complexes with such ligands. The results show that the active aldehyde derivatives of thiamin, 2-(α-hydroxylbenzyl)- and 2-(α-cyclohexylmethyl)thiamine, very easily form complexes with group IIB metals,[13] as well as first-row transition metals,[14] all coordinated to the N(1') site of the pyrimidine moiety. The IIB metals resemble the alkaline-earth metals, Mg^{2+} being the essential element in thiamin activity; and the first-row transition metals have been reported to be active in vitro.[1]

The structure of the complex Hg(2-(α-hydroxybenzyl)thiamine)Cl₃ is also reported here. To our knowledge, this is the

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Table I. Summary of Crystal Data and Refinement Results for Hg(HBT)Cl₃·H₂O

space group	$P2_1/n$ (monoclinic)
a, Å	9.588 (6)
b, Å	7.644 (3)
c, Å	31.412 (20)
β, deg	90.41 (5)
V, Å³	2303 (2)
molecules/unit cell	4
MW	696.0
cryst dimens, mm	0.5 × 0.14 × 0.02
calcd density, g cm⁻³	2.008
data collectn wavelength, Å	1.5418
sin θ/λ limit, Å⁻¹	0.539
total no. of reflctns measd	3125
no. of independent reflctns	3124
no. of reflections used, $1 > 3\sigma(1)$	2408
no. of variable params	280
final agreement factors	$R(F) = 0.0527$
	$R(wF) = 0.0683$

first crystal structure ever reported of an active aldehyde derivative of thiamin.

A preliminary account of this work has been published.[13]

Experimental Section

Thiamin chloride hydrochloride was purchased from Sigma Chemical Co. and used without further purification. ZnCl₂, CdCl₂, and HgCl₂ and all other chemicals used were from Aldrich AG. The ligands 2-(α-hydroxybenzyl)thiamin and 2-(α-hydroxy-α-cyclohexylmethyl)thiamin were prepared as described in the literature.[15]

Preparation of the compounds MLCl₃: where M is Zn^{2+}, Cd^{2+}, and Hg^{2+}; and L is one of the two active aldehyde derivative monocations of thiamin, (HBT, HCMT).

All the complexes were prepared by mixing equimolar (1 mmol) amounts of the ligands and the metal chlorides, in methanolic solutions for the 2-(α-hydroxybenzyl)thiamin complexes and in equal volumes of ethanol–methanol solutions for the 2-(α-hydroxy-α-cyclohexylmethyl)-thiamin complexes. Only the complex Hg(HBT)Cl₃ was prepared in aqueous solution. The ligands, originally in their hydrochloride forms, were neutralized by first adding an equivalent amount of 0.1 N KOH solution and filtering off the KCl formed, in cases in which methanol was used as a solvent. This was done prior to the addition of the metal chlorides, so as to free the N(1') positions of the pyrimidine rings. Addition of the metal chlorides resulted in white precipitates being formed, which were then washed with small quantities of methanol and ether and dried: first at room temperature, followed by drying at 60 °C under vacuum. The yields were ~40%. The elemental analyses agreed with the assigned formulas.

The molar conductance values (determined in concentrations of 10⁻³ M at 20 °C in DMF with a Conductoscope E365) are initially lower than values expected for a 1:1 electrolyte,[16] but they increase with time, indicating replacement of one or more chloride by solvent molecules. In aqueous solutions, however, all the chloride ligands are replaced immediately, as indicated by ΛM values of ~300 Ω^{-1}·cm⁻²·mol⁻¹, corresponding to 1:3 electrolytes.[16]

The bromo analogues of all the complexes of the type MLBr₃ were prepared from the chloro analogues, after treatment with an excess of Br⁻ ion. Suspensions of all the chloro complexes in methalonic solutions were treated with an excess of (CH₃)₄NBr for 24 h, except the complex Hg(HBT)Cl₃, which was suspended in an aqueous solution and treated with KBr for 24 h.

The deuterated ligands and complexes were prepared either by carrying out their preparations in D₂O or MeOD or by dissolution of the nonlabeled compounds in D₂O and reprecipitation with a mixture of acetone and ether.

The IR spectra were recorded on a Perkin-Elmer 597 instrument in KBr pellets or Nujol mulls. The far-IR spectra were taken in a Brucker IFS 113y Fourier transform spectrophotometer in polyethylene pellets.

Crystal Structure. Crystals of the compound Hg(2-(α-hydroxybenzyl)thiamin)Cl₃, suitable for X-ray analysis, were obtained by slowly mixing an aqueous suspension of HgCl₂ with a suspension of the ligand in silica gel, in a volumetric cylinder. The crystals appeared in the interface of the two suspensions several days after mixing.

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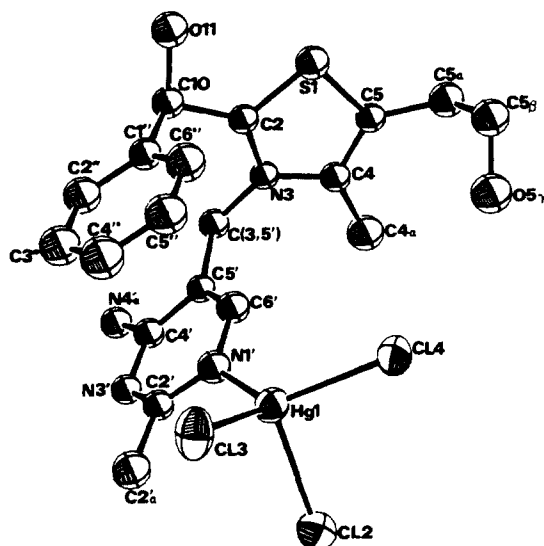(16) Geary, W. K. *Coord. Chem. Rev.* **1971**, *7*, 81–122.

Figure 1. Crystal structure of the complex Hg(HBT)Cl₃.

A needlelike crystal of 0.5 × 0.14 × 0.02 mm was mounted on a glass fiber. A Siemens/Nicolet/SyntexP2₁ automated four-circle diffractometer, with Cu Kα radiation and a graphite crystal monochromator, was used for intensity data collection. The unit cell parameters were determined by least-squares fit of 15 centered reflections. Data were collected by the ω scan technique for all reflections such that $10.0° < 2\theta < 110.0°$. Throughout the data collection three reflections were monitored periodically and no decay was observed. Of 3125 reflections collected, 2408 reflections with $I > 3\sigma(I)$ were retained for the ensuing structure analysis. These reflections were corrected for Lorentz, polarization, and absorption effects.

The compound crystallizes in the monoclinic space group $P2_{1/n}$, with the following cell parameters: a = 9.588 (6) Å, b = 7.644 (3) Å, c = 31.412 (20) Å, β = 90.41 (5)°. The structure was solved by direct methods using the SHELX-86 system of crystallographic programs. The positions of the mercury atom and three chlorine atoms were revealed in the initial E map. Subsequent difference-Fourier maps revealed all the remaining light atom positions. Least-squares refinement of the atomic coordinates and thermal parameters resulted in final agreement values of R = 5.72% and R_w = 6.83%. Details of crystal data and collection are listed in Table 1. A drawing of the complex and the labeling scheme is given in Figure 1.

Results and Discussion

IR Spectra. Strong indications for the existence of a direct M–N(1') bond and the noninvolvement of the NH₂ group in metal bonding are given from an examination of the IR spectra in the region of 1600–1700 cm⁻¹. The free ligand 2-(α-hydroxybenzyl)thiamin chloride hydrochloride (HBT·Cl) shows bands at 1670 and 1640 cm⁻¹, which are assigned to a coupling between the δ(NH₂) and ν(C=N) motions of the pyrimidine ring, since they are replaced upon deuteration by a unique band at 1660 cm⁻¹, solely due to ν(C=N).[9,17,18] The nonprotonated ligand (HBT) shows these bands at 1680 and 1610 cm⁻¹, which were replaced by one band at 1615 cm⁻¹ upon deuteration. In contrast, in the second ligand 2-(α-hydroxy-α-cyclohexylmethyl)thiamin chloride hydrochloride (HCMT·HCl) the two bands observed at 1660 and 1605 cm⁻¹ have pure ν(C=N) character and δ(NH₂) character, respectively, since only the band at 1660 cm⁻¹ is observed upon deuteration. In the deprotonated form (HCMT), the sequence is reversed; of the two bands at 1655 and 1605 cm⁻¹, it is only the first that disappears upon deuteration, due to a pure δ(NH₂) motion, while the second band (unchanged upon deuteration) is a pure ν(C=N) ring motion. This is consistent with a 40–50-cm⁻¹ shift to higher frequencies of the ν(C=N) motion of the pyri-

Table II. Bond Distances in Hg(HBT)Cl₃·H₂O and the Ligand HBT[a]

| | distances, Å | | | distances, Å | |
bonds	Hg(HBT)Cl₃	HBT	bonds	Hg(HBT)Cl₃	HBT
Hg1–C12	2.588 (3)		C4–C4α	1.48 (1)	1.494
Hg1–C13	2.425 (3)		C4–C5	1.38 (1)	1.366
Hg1–C14	2.484 (3)		S1–C5	1.72 (1)	1.733
Hg1–N1'	2.23 (1)		C5–C5α	1.49 (1)	1.487
N1'–C2'	1.35 (1)	1.335	C5α–C5β	1.56 (2)	1.513
C2'–C2'α	1.51 (2)	1.477	C5β–O5γ	1.44 (2)	1.415
C2'–N3'	1.32 (1)	1.314	S1–C2	1.69 (2)	1.670
N3'–C4'	1.35 (1)	1.353	C2–C10	1.51 (1)	1.506
C4'–N4'α	1.37 (1)	1.310	C1''–C10	1.52 (2)	1.511
C4'–C5'	1.41 (2)	1.430	C10–O11	1.42 (2)	1.447
C(3,5')–C5'	1.50 (1)	1.503	C1''–C2''	1.41 (2)	1.399
N1'–C6'	1.35 (1)	1.345	C2''–C3''	1.36 (2)	1.372
C5'–C6'	1.37 (2)	1.359	C3''–C4''	1.41 (2)	1.366
C5'–C(3,5')	1.50 (1)	1.503	C4''–C5''	1.42 (2)	1.382
N3–C(3,5')	1.49 (1)	1.478	C1''–C6''	1.37 (2)	1.371
C2–N3	1.32 (1)	1.343	C5''–C6''	1.42 (2)	1.396
N3–C4	1.39 (1)	1.398			

[a] Taken from ref 12b.

midine ring upon protonation,[19] a phenomenon that has been observed in other similar cases.[7a,9,17,18] In the corresponding complexes M(HBT)Cl₃, the bands are (a) with Hg²⁺ at 1665 and 1620 cm⁻¹ upon deuteration; (b) with Cd²⁺ at 1665 and 1620 cm⁻¹, replaced by one at 1625 cm⁻¹ upon deuteration; and (c) with Zn²⁺ at 1670 and 1625 cm⁻¹, replaced by one at 1630 cm⁻¹ upon deuteration. Finally, in the series M(HCMT)Cl₃, the bands appear at 1645 and 1620 cm⁻¹ for the Hg²⁺ complex, 1645 and 1625 cm⁻¹ for the Cd²⁺ complex, and 1645 and 1628 for the Zn²⁺ complex, the highest of which are removed upon deuteration.

It is observed that in all the complexes, the ν(C=N) motions are in intermediate frequencies of the nonprotonated and protonated ligands $\nu[(C=N)L·HCl] > \nu[(C=N)MLCl_3] > \nu[(C=N)L]$. The δ(NH₂) band follows the inverse order $\delta[NH_2(L)] > \delta[NH_2(MLCl_3)] > \delta[NH_2(L·HCl)]$. This implies a metalation at the (N1') site of the pyrimidine ring of the ligand in the complexes studied.[9,17,19a,c] In addition, the positions of the δ(NH₂) bands imply the absence of direct bonding of these metals with this amino group. Note, that the shift to higher frequencies of the metalated ν(C=N) motions decreases with the heavier metal atom and follows the order $\nu[(C=N)ZnLCl_3] > \nu[(C=N)CdLCl_3] > \nu[(C=N)HgLCl_3]$. Also, note that all the δ(NH₂) and ν(C=N) bands of the ligand HBT, its protonated form, and its metal complexes are all observed at higher frequencies than the corresponding motions of the ligand HCMT, most probably as a result of an intramolecular stacking interaction between the pyrimidine and the benzyl ring in HBT, observed also in the crystal structure of the complex Hg(HBT)Cl₃.

It is finally noted that the IR spectra of all of the complexes of Zn²⁺, Cd²⁺, and Hg²⁺ with HBT were similar band by band, as well as the complexes of the same metals with HCMT, except the M–Cl stretching frequencies. This indicates a similarity of the structures of all the compounds in the solid state to the Hg-(HBT)Cl₃ complex whose structure is reported here.

Crystal Structure. This is the seventh crystal structure of a thiamin derivative showing direct metal–ligand bonding.[6e,7h,10]

The unit cell contains 4 molecules and an equal number of water molecules of crystallization. These are stabilized with inter- and intramolecular forces that are a mixture of hydrogen bonds and electrostatic and stacking interactions.

The bond distances and bond angles of the complex are included in Tables II and III. Tables II and III also contain the corresponding distances and angles of the free ligand, taken from ref 12b, for comparison purposes.

An intermediate stacking interaction exists between the aromatic rings of pyrimidine and benzyl, which are almost parallel at a distance of 3.46 Å and a dihedral angle of 9° (8.9° in the

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Table III. Bond Angles in Hg(HBT)Cl₃·H₂O and the Ligand HBT[a]

bonds	Hg(HBT)CX₃	HBT
C12–Hg1–C13	105.8 (1)	
C12–Hg1–C14	99.0 (1)	
C13–Hg1–C14	106.4 (1)	
N1′–Hg1–C12	98.7 (2)	
N1′–Hg1–C13	117.6 (2)	
N1′–Hg1–C14	125.3 (2)	
N1′–C2′–C2′α	118.1 (10)	117.3
N1′–C2′–N3′	124.0 (10)	122.3
C2′α–C2′–N3′	117.9 (10)	120.3
C2′–N3′–C4′	117.9 (9)	118.9
N3′–C4′–N4′α	115.1 (9)	117.1
N3′–C4′–C5′	122.6 (10)	120.6
N4′α–C4′–C5′	122.3 (10)	122.3
C4′–C5′–C6′	114.3 (10)	116.9
C4′–C5′–C35′	118.5 (9)	120.1
C35′–C5′–C6′	127.1 (9)	122.9
N1′–C6′–C5′	124.1 (10)	120.1
N3–C35′–C5′	114.0 (9)	112.9
C4–N3–C35′	122.2 (9)	122.5
C2–N3–C35′	122.2 (9)	124.0
C2–N3–C4	114.5 (8)	113.5
C5–C4–N3	111.6 (9)	112.4
C5α–C5–C5	128.5 (10)	128.2
C5β–C5α–C5	111.9 (9)	114.0
O5γ–C5β–C5α	110.6 (9)	108.5
C10–C2–N3	126.9 (9)	125.1
C1″–C10–C2	110.0 (9)	112.5
C2″–C1″–C10	119.0 (1)	121.2
C6″–C1″–C10	121.5 (10)	119.1
C6″–C1″–C2″	119.5 (11)	119.6
C3″–C2″–C1″	121.2 (12)	120.5
C4″–C3″–C2″	120.0 (12)	120.8
C5″–C4″–C3″	120.1 (13)	119.7
C6″–C5″–C4″	118.0 (13)	119.7
C5″–C6″–C1″	121.1 (11)	121.1
C2′–N1′–C6′	117.0 (1)	
Hg1–N1′–C6′	123.4 (7)	
Hg1–N1′–Cl′	119.8 (7)	

[a] Taken from ref 12b.

free ligand).[12b] The presence of the Hg²⁺–N(1′) coordination does not seem to influence such intermolecular stacking interactions, which also exist in the crystal structure of the uncomplexed free ligand.[12b] The closest intermolecular ring contact in the Hg complex occurs between C(2″) and C(5′) with a separation of 3.400 Å. The closest such contact in the free ligand is 3.381 Å, occurring between C(2″) and C(4′).[12b]

On the other hand, in the Hg complex one does not observe any intramolecular stacking interaction between the other aromatic rings (i.e., benzyl···benzyl) and especially between the pyrimidine rings, which are known to orient themselves in a head-to-tail arrangement in other similar structures.[7h,10]

Additional strong interactions include hydrogen bonds and electrostatic dipole–dipole interactions, given in Table IV. Distances longer than 4 Å are not included. A few relevant interactions are shown in Figure 2.

The N(4′α)–Cl(2) distance of 3.32 Å found in the present structure falls in the range of 3.12–3.44 Å[7h] of other similar structures.[7,10] The strongest hydrogen bonding exists between a water of hydration and the O(5γ) atom. The N(4′α) atom participates in hydrogen bonding with the N(3′) and the Cl(2) atoms. The hydrogen atom at O(11) also takes part in bonding with a chlorine atom[12b] and is labile.

The shortest electrostatic contact occurs between the S(1) and O(11) atoms [2.79 (1) Å], very close to the value observed in the crystal structure of the free ligand (2.764 Å).[12b] The corresponding φₛ[S(1)–C(2)–C(10)–O(11)] torsional angle is 10.5°, comparable to 8.4° of the free ligand.[12b] It was found to be 20.6° in the structure of 2-(α-hydroxyethyl)thiamin[12b] with an S(1)–O(11) contact distance of 2.852 Å. This implies a partial positive charge migration to the S(1) atom in the active aldehyde derivatives of thiamin,[12] in agreement with the theoretical calculations of Jordan.[20] The N(3)···Cl(4) closed-contact distance of 3.41 (1) Å,

Table IV. Possible Hydrogen-Bonding Interactions and Other Short Contacts in Hg(HBT)Cl₃·H₂O

| A[a]	B	equivalent position of B	A–B, Å
		Hydrogen Bonds	
N(3′)	N(4′α)	1 + x, y, −z	3.13 (1)
N(4′α)	Cl(2)	x, y, z	3.32 (1)
N(4′α)	N(3′)	x, y, z	3.29 (1)
O(11)	Cl(2)	0.5 − x, 0.5 + y, 0.5 − z	3.01 (1)
O(12)	Cl(4)	1 − x, 1 − y, 1 − z	3.08 (1)
O(12)	O(5γ)	1 − x, 1 − y, 1 − z	2.69 (1)
O(12)	O(5γ)	x − 0.5, 0.5 − y, 0.5 + z	2.76 (1)
		Electrostatic Contacts	
S(1)	O(12)	x − 0.5, 0.5 − y, 0.5 + z	3.65 (1)
S(1)	O(5γ)	x, y, z	3.86 (1)
S(1)	O(5γ)	1.5 − x, y − 0.5, 0.5, 0.5 − z	4.18 (1)
S(1)	O(11)	x, y, z	2.79 (1)
C(10)	Cl(2)	1 + x, 1 + y, z	3.77 (1)
C(10)	Cl(3)	1 + x, y, z	3.64 (1)
N(3)	Cl(4)	1 + x, y, z	3.41 (1)
C(4α)	Cl(4)	x, y, z	3.90 (1)
C(3,5′)	Cl(2)	1 + x, y, z	3.73 (1)
C(3,5′)	Cl(3)	1 + x, y, z	3.77 (1)
C(3,5′)	Cl(4)	1 + x, y, z	3.60 (1)
C(2α)	Cl(2)	x, y, z	3.63 (1)
C(2α)	Cl(3)	x, y, z	3.77 (2)
C(5β)	Cl(2)	1.5 − x, 0.5 + y, 0.5 − z	3.73 (1)
C(5β)	Cl(4)	1.5 − x, 0.5 + y, 0.5 − z	3.78 (1)
C(4)	Cl(2)	1 + x, y, z	3.76 (1)

[a] O(12) is the oxygen atom of the water molecule of crystallization.
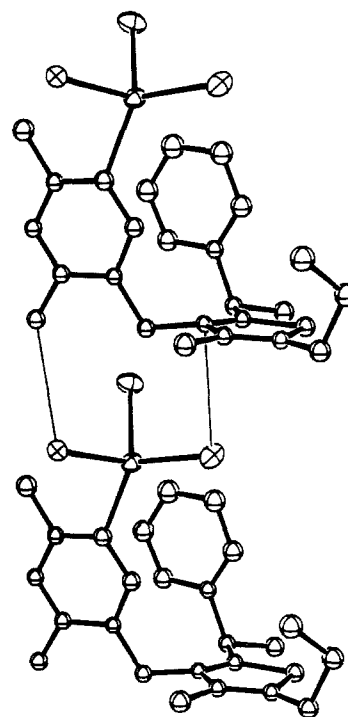
Figure 2. Perspective view of Hg(HBT)Cl₃·H₂O showing "two-point bridge" (thin line) close contacts between two adjacent pairs of molecules.

however, suggests the presence of a residual positive charge remaining on N(3).

The coordination around Hg²⁺ is pseudotetrahedral with normal Hg–N and Hg–Cl bond distances. The Hg–N(1′) bond distance of 2.23 (1) Å implies a strong interaction. The bond distances of the Hg–Cl bonds follow the order Hg–Cl(2) > Hg–Cl(4) > Hg–Cl(3). This is expected since (a) the Cl(2) atom participates in two hydrogen bonds with N(4′α) and O(11), while (b) the Cl(4) atom forms only one H bond with the water of hydration, and (c) the Cl(3) atom is involved in no H bonds. This makes the angle N(1′)–Hg(1)–Cl(2) = 98.7 (2)° to be less than the tetra-

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Zn^{+2}, Cd^{+2}, and Hg^{+2} Interaction with Thiamin Derivatives

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hedral value of 109.5° and the N(1')–Hg–Cl(4) = 125.3 (2)° and N(1')–Hg–Cl(3) = 117.6 (2)° angles to be greater.

The C(2')–N(1')–C(6') angle of 117.0 (1)° is due to the Hg–N(1') coordination and differs slightly from the corresponding value of 116.5 (2)° of Cd(thiamin)Cl$_3$·0.6H$_2$O,[10a] 115.6 (3)° for Zn(thiamin)Cl$_3$·0.4H$_2$O,[10d] 118.0 (10)° for Pt(thiamine)Cl$_3$·H$_2$O,[7h] etc. This is due to the different acid strength and softness of the various metal ions toward the N(1') site.[10b] The C(4')–N(4'α) bond distance of 1.37 (1) Å in the present structure is the longest found in crystal structures of metal thiamin complexes with M–N(1') bonding.[7b,10] This result is expected since the bulky HgCl$_3^-$ anion is expected to increase the C(4')–N(4'α) distance by decreasing the contribution of resonance structure II, proposed by Kraut and Reed,[21] more than protonation.[10b]

II
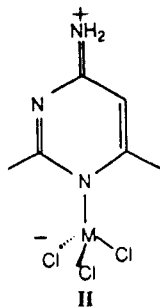
The angle between the pyrimidine and thiazolium planes is almost prependicular with a value of 87.9°. This angle is 82.2° in the structure of Zn(thiamin)Cl$_3$[10d] and 88.4° in the structure of Cd(thiamin)Cl$_3$.[10a] It is also larger than the one found in the free ligand (84.9°).[12b] It was suggested[21] that this angle is of importance in the oxidation of thiamin to thiochrome, influencing the biological action of thiamin. This angle is found to be 75.3° in the structure of Cu(thiamin)Cl$_2$,[10b] 76° in the structure of thiamin chloride hydrochloride,[22] and 74.4° in the bis(protonated)thiamin tetrachlorodioxouranium(VI).[7b] [Cu^{2+} is known to oxidize thiamin,[10b] as well as 2-(α-hydroxybenzyl)thiamin].[14] It is found however to be 104.7° in the isostructural bromo complex Cu(thiamin)Br$_2$.[10d]

The relative orientation of the pyrimidine and thiazolium rings depends upon the torsional angles defined according to Pletcher and Sax.[22] The observed values of ϕ_P = [N(3)–C(3,5')–C(5')–C(4')] = 172.7° and ϕ_T = [C(5')–C(3,5')–N(3)–C(2)] = –100.0° in the present crystal structure correspond to the less common S conformation, usually found in C(2)-substituted thiamin derivatives.[12] It was proposed that the S(1)···O(11) electrostatic interaction is responsible for the S conformation of the C(2) substituent of thiamin.[12] The S conformation was also found in the structures of [thiamin][CdCl$_4$]·H$_2$O[7d] (ϕ_P = 137.3°, ϕ_T = 110.4°), Zn(thiamin)Cl$_3$·0.4H$_2$O,[10d] (ϕ_P = 113.4°, ϕ_T = 130.4°), Cd(thiamin)Cl$_3$·0.6H$_2$O[10a] (ϕ_P = +129.8°, ϕ_T = +112.6°, and [thiamin][HgCl$_4$]·H$_2$O[7g] (ϕ_P = 179°, ϕ_T = –103°). In the C-(2)-substituted thiamins it is ϕ_P = –145.6°, ϕ_T = –100.3° for 2-(α-hydroxyethyl)thiamin chloride hydrochloride[12a] and ϕ_P = –167.3°, ϕ_T = 92.7° for 2-(α-hydroxybenzyl)thiamin chloride hydrochloride.[12b]

Shin et al.[23] argued that "the conformation of thiamin is largely influenced by intramolecular properties". Also, Richardson et al.[7d] suggested that the conformation of thiamin is the result of packing forces in the crystal. The energy difference between the F and the S conformers is very small according to the potential energy calculations of Jordan.[20] Cramer et al.[7h] concluded that the preference of an S or F conformation depends mainly on the Cl···Cl nonbonding distance, in compounds with polychlorometal anions. Thus, the F form is favored by small metal anions (CuCl$_2^-$) having an average Cl···Cl nonbonding distance of 3.4 Å, while larger metal anions (CdCl$_3^-$), (ZnCl$_3^-$) with Cl···Cl

distance averages of 3.9 Å favor the S form. In the present structure, the shortest Cl···Cl nonbonding distance is 3.857 (5) Å in agreement with this observation. However, it is not known if the S conformation is implied by (a) the ligand itself, being a C(2) substituent of thiamin which in turn produces the long Cl···Cl distance, (b) if the bulky (HgCl$_3^-$) group imposes the S conformation, or (c) if both factors operate simultaneously in the present case. In contrast, the crystal structure of Cu(thiamin)Br$_2$[10e] is an exception to this rule, having a Br···Br nonbonding distance of 3.995 Å and adopting the F conformation.

The torsion angles that describe the conformation of the β-hydroxyethyl side chain[23] are the $\phi_{5\alpha}$ = [S(1)–C(5)–C(5α)–C(5β)] = 78.6° and $\phi_{5\beta}$ = [C(5)–C(5α)–C(5β)–O(5γ)] = 65.5°, implying a long intramolecular S(1)···O(5γ) contact distance of 3.86 (1) Å in the present case. These angles are much smaller in the case of HBT[12b] with $\phi_{5\alpha}$ = 3.3°, $\phi_{5\beta}$ = 63.4°, and S(1)···O(5) = 3.003 Å. These molecular parameters are $\phi_{5\alpha}$ = 46.5°, $\phi_{5\beta}$ = –68.8° in Cd(thiamin)Cl$_3$·0.6H$_2$O,[10a] with S(1)···O(5γ) = 2.879 Å; and $\phi_{5\alpha}$ = 45°, $\phi_{5\beta}$ = –67.6° in Zn(thiamin)Cl$_3$·0.4H$_2$O[10d] with S-(1)···O(5γ) = 2.878 Å. In the present case the value of $\phi_{5\alpha}$ that approaches 90° does not allow a close S(1)···O(5γ) contact distance and the C(5α)–C(5β) bond is oriented approximately perpendicular to the thiazolium ring.[12b] Thus, the S(1)···O(5γ) distance of 3.86 (1) Å is the longest such distance found in this class of compounds. It is also much longer than the corresponding distance in the free ligand.[12b] This comparatively weak interaction does not seem to influence the C(5β)–O(5γ) bond distance, being 1.44 (1) Å in the present case and longer than the one observed in the crystal structure of Cd(thiamin)Cl$_3$·0.6H$_2$O[10a] (1.437 Å), which has a strong S(1)···O(5γ) interaction (2.879 Å).[10a] In addition, the C(2)–S and C(5)–S distances of 1.69 and 1.72 Å, respectively, in the title compound are comparable to the ones observed in the structure of Cd(thiamin)Cl$_3$·0.6H$_2$O.[10a]

A second S(1)···O(5γ) distance to a neighboring molecule of 4.18 (1) Å is observed, contributing to the interaction observed between the two molecules. This comparatively short distance may also account for the large intramolecular distance S(1)···O-(5γ) of 3.86 (1) Å.

Conclusion

The most important qualitative observation in this study, we believe, is the very facile formation of such complexes of active aldehyde derivatives of thiamin with metals, bonded to the N(1') position of the pyrimidine ring of thiamin, which takes place not only with IIB bivalent metal ions, but also with first-row transition metals.[14] These complexes are formed by the simple mixture of the metal chlorides with both ligands, in stoichiometric amounts, in aqueous or methanolic solution,[24] while such mixtures with thiamin alone are known to produce only salt-type complexes.[7a-g] This should be due to the migration of a large amount of positive charge, formerly located at N(3), to the S(1) atom of HBT, exemplified by the strong interaction S(1)···O(11).[1,12,20] This indicates that the intervention of metals in the enzymatic action of thiamin should follow the formation of the active aldehyde intermediates.

In the decomposition of the metal-complexed active aldehyde intermediate it was proposed that the metal coordination should favor the V conformation, which approaches the N(4'α)H$_2$ group near the C(2) or O(11)–H atoms, thereby acting either as a proton acceptor[5] or a proton donor.[25] The O(11)–H proton was proposed to deprotonate in the mechanism of Breslow[3] and has a low pK_a value.[26] However, in no structure of thiamin or any of its derivatives has such a conformation been found, except that of oxythiamin[27] known to form active aldehyde intermediates but not participating in further reactions.[5]

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(24) Preliminary stability constant determinations show that the affinity of Cd^{2+} toward the active aldehyde derivatives of thiamin is larger by a factor of 10^2, compared with thiamin itself.

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Since all the crystal structures of thiamin, its derivatives, and their metal complexes are mostly in the F configuration, with only a few exceptions in the S configuration, including its active aldehyde derivatives, the role of the $N(4'\alpha)$–H_2 group to act directly as a proton donor or acceptor is questionable. As pointed out by Sax et al.,[12a] the deprotonation of the O(11)–H proton makes the S(1)···O(11) interaction even stronger and stabilizes the preferred S conformation. Thus, the S(1) atom is better suited sterically and electronically to facilitate this deprotonation than the frequently mentioned $N(4'\alpha)$ amino group.[12b] Since Hg^{2+} coordination and (more generally), metal coordination *follows* the formation of the active aldehyde derivative of thiamin, thereby *not* influencing the original S conformation,[28] it seems reasonable to accept this hypothesis. To provide further confirmation,

however, the elucidation of many similar structures will have to be done.

Supplementary Material Available: Tables of final temperature factors (Table A), final atomic coordinates (Table B), best-weighted least-squares planes for the pyrimidine, thiazole, and benzyl rings (Table C), and intramolecular separations between pairs of atoms (Table D), and figure of the unit cell packing diagram for the complex Hg(HBT)Cl₃·H₂O (4 pages). Ordering information is given on any current masthead page.

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(28) All the complexes of the 11B group metals, as well as the first row transition metals (Co²⁺, Ni²⁺, etc.), with these ligands are isostructural in the solid state, having identical (band by band) IR and Raman spectra.

The Tetranuclear Trianion [Fe₄Te₄(SC₆H₅)₄]³⁻: Crystal and Molecular Structure and Magnetic Properties

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Contribution from the Dipartimento di Chimica, Università di Firenze, and I.S.S.E.C.C., C.N.R., Firenze, Italy. Received November 6, 1989

Abstract: The synthesis and the spectroscopic, magnetic, and structural characterization of the compound (Et₄N)₃[Fe₄Te₄(SPh)₄] (Ph = C₆H₅) are reported. The complex crystallizes in the orthorombic system, space group *Fdd2*, with $a = 39.976$ (5) Å, $b = 24.963$ (6) Å, and $c = 12.200$ (2) Å. The molecular structure consists of discrete tetranuclear anions [Fe₄Te₄(SPh)₄]³⁻ with a cubane-like [Fe₄Te₄]⁺ unit. The magnetic behavior has been interpreted by using the Heisenberg–Dirac–Van Vleck exchange coupling model with antiferromagnetic interactions between the iron centers. The ground state has been found to correspond to a total spin state $S = 3/2$. EPR and ¹H-NMR spectra are also reported. The available magnetic data of Fe₄S₄ and Fe₄Se₄ clusters have also been interpreted providing the correct ground state. The increased distance between the irons in the [Fe₄Te₄]⁺ core in comparison to the analogous [Fe₄S₄]⁺ and [Fe₄Se₄]⁺ cores decreases the antiferromagnetic coupling among the iron ions. The influence of geometric parameters on the exchange pathways between iron atoms in this class of compounds is discussed within the orbital model of the exchange interaction using EHMO theory.

Introduction

The synthesis of low molecular weight analogues of four iron ferredoxins and the study of their spectroscopic, magnetic, and structural properties have been the subject of extensive investigations.[1] From all these studies the isoelectronic nature of the synthetic clusters with Fe–S proteins which occur in important biological redox processes has appeared.[2–4]

Despite the number of experimental and theoretical efforts, the electronic structure of these systems is still not completely determined, and an active area of research is devoted to the synthesis of new clusters which could be investigated with the largest possible numbers of experimental techniques in order to get a deeper insight into their electronic structure. In the case of Fe₂S₂ proteins and in their synthetic analogues the low-lying energy levels have been successfully interpreted within the Heisenberg–Dirac–Van Vleck exchange coupling theory, which reduces the electronic coupling between the individual iron centers to a formal magnetic coupling between localized spins.[5] In a number of Fe₃S₄ clusters and proteins Mössbauer and magnetically perturbed Mössbauer studies have shown that some electron delocalization should occur.[6] In

particular the magnetic structure unit Fe₃S₄⁺, formally containing one Fe(III) and two Fe(II) centers, has been interpreted assuming complete valence delocalization between two iron centers and exchange interaction of this delocalized couple with the other iron center.[6] A similar picture has been adopted to describe the nature of the low-lying energy levels in some Fe₄S₄ clusters.[7]

With the aim to provide new information for the understanding of the properties of the Fe₄X₄ clusters we wish to report here the synthesis, crystal and molecular structure, and magnetic and spectroscopic properties of (Et₄N)₃[Fe₄Te₄(SPh)₄], a molecule

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